UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION **This document relates to**: *Track Three Cases*	**MDL No. 2804** **Case No. 17-md-2804** **Judge Dan Aaron Polster**

DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

EXHIBIT 13

have little excess cardiovascular risk and do not typically require medication. ABPM can also be used to monitor the effectiveness of drug treatment and to detect the occasional patient with normal office blood pressures but elevated blood pressures out of the office ("masked hypertension"). Despite the availability of ambulatory monitors, policies that support reimbursement and current recommendations to use it routinely the use of ABPM in the United States remain quite low.

Self-monitoring of blood pressure, however, has become quite common, and many clinicians and patients see it as a more practical approach to out-of-office monitoring than ABPM. Unfortunately, the practice of home blood pressure monitoring (HBPM) is even less standardized and less supported by evidence than ABPM. Correct HBPM requires patient training, correct equipment, and correct interpretation of results. The techniques that define best practice office measurement are also relevant at home but are rarely followed. HBPMs are also typically lower than office measurements but the relationship is not uniformly predictable. The exact timing of measurement is also important. Current guidelines suggest measurement in the morning before medications and before supper, but this is not uniform practice. The ability of HBPM to predict cardiovascular risk is less than ABPM, and the correlation of HBPM with ABPM to diagnose white coat hypertension is only 60% to 70%. Moreover, clinical trials of home monitoring alone to improve blood pressure control have shown little effect on BP at 6-month and 1-year follow-ups.

What, then, is a reasonable approach to blood pressure measurement in 2018? Primary care practices should develop a clear strategy for best practice office measurement. Revisions of staff training, work flow, and physical settings may be needed. Blood pressure measurement should comply with the best practice check list. Practices may want to also consider implementing systems more similar to those used in clinical trials, in which unobserved automatic measurement is used. If an initial blood pressure measurement is high, a repeated measurement is indicated. Although this can be done by medical assistants, patients appreciate the primary care clinicians who retake the blood pressure measurement themselves. This may be the most important part of that day's physical examination. Practices also need to decide which measurement should be recorded in the medical record. Although most clinical trials and practice guidelines suggest averaging blood pressure measurements, quality improvement guidelines commonly use the final blood pressure recording.

Home blood pressure monitoring can be a useful adjunct to care for some patients, but it, too, must be used carefully. It may identify white coat hypertension and may help adherence and control for individual patients. Multiple measurements over the course of an occasional single day (akin to ABPM) may be preferable to daily measurements at the same time of each day. This is especially true given the diurnal and other variations of blood pressure that most patients experience.

ABPM should be used more than it currently is. It is not clear that it is needed in every patient (as suggested by current guidelines), but it certainly can be useful in a larger number of patients. Finding even a few patients in each primary care practice who do not need medications is well worth it. This may be especially true in patients with lower cardiovascular risk. Conversely, ABPM may be useful to confirm good control throughout the day in high-risk patients, especially those with existing cardiovascular disease.

As we continue to debate the thresholds and goals of high blood pressure treatment, we will need to better explain to patients the benefits and harms of each approach and solicit their preferences. The least we can do is better define their risk with better measurement of blood pressure.

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Published Online: April 16, 2018. doi:10.1001/jamainternmed.2018.0311

Conflict of Interest Disclosures: None reported.

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Association of Pharmaceutical Industry Marketing of Opioid Products to Physicians With Subsequent Opioid Prescribing

Despite the increasing contribution of heroin and illicitly manufactured fentanyl to opioid-related overdose deaths in the United States, 40% of deaths involve prescription opioids.[1] Prescription opioids are commonly the first opioid encountered in a trajectory toward illicit consumption.[2] Although opioid prescribing has declined nationally, rates in 2015 were triple those in 1999 and remain elevated in regions of the country with higher numbers of overdoses.[3]

Related articles pages 759 and 764

Pharmaceutical industry marketing to physicians is widespread, but it is unclear whether marketing of opioids influences prescribing.[4] We studied the extent to which pharmaceutical industry marketing of opioid products to physicians during 2014 was associated with opioid prescribing during 2015.

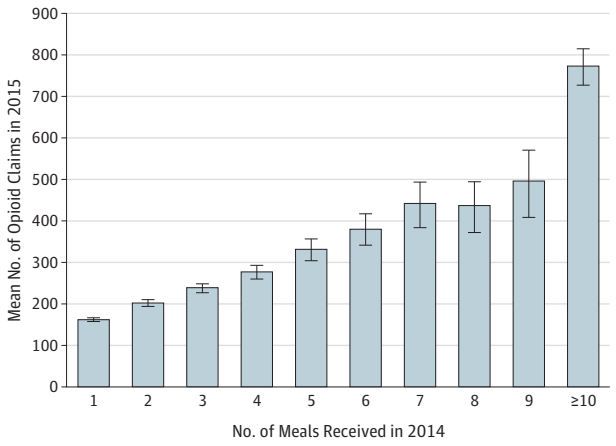
Table. Industry Opioid Marketing in 2014 and Opioid Prescription Claims for Medicare Beneficiaries in 2015

Specialty	Physicians, No.	Total Payments, $ (%)	Received ≥1 Payment in 2014, No. (%)	Opioid Claims in 2015, Mean (SD)		Adjusted Relative Difference in Claims Attributable to Receipt of Any Payment, % (95% CI)[a]
				Did Not Receive Payment	Received ≥1 Payment	
Overall	369 139	9 071 976 (100.0)	25 767 (7.0)	134 (281)	539 (945)	9.3 (8.7 to 9.9)
Pain medicine	2565	2 914 912 (32.1)	1424 (55.5)	876 (1301)	1700 (1943)	1.2 (−0.9 to 3.4)
Physical medicine and rehabilitation	4599	1 818 627 (20.0)	1385 (30.1)	264 (608)	1071 (1597)	5.4 (2.8 to 8.1)
Anesthesiology	2294	1 417 763 (15.6)	933 (40.7)	500 (976)	1525 (1908)	2.7 (−0.3 to 5.7)
Internal medicine and subspecialties, except hematology-oncology	82 377	785 916 (8.7)	6371 (7.7)	171 (285)	503 (609)	7.2 (6.0 to 8.3)
Family medicine	68 950	746 215 (8.2)	8376 (12.2)	213 (309)	460 (564)	6.2 (5.2 to 7.2)
Hematology-oncology	8053	452 345 (5.0)	832 (10.3)	108 (127)	165 (183)	3.4 (0.6 to 6.2)
Neurology	5221	358 491 (4.0)	722 (13.8)	101 (263)	541 (998)	11.5 (7.7 to 15.5)
Orthopedic surgery	16 313	165 740 (1.8)	2296 (14.1)	135 (172)	252 (424)	2.7 (1.5 to 3.8)
General and subspecialty surgery	33 247	173 416 (1.9)	2164 (6.5)	56 (76)	95 (237)	2.9 (1.4 to 4.3)
Radiation-oncology	1729	136 590 (1.5)	169 (9.8)	34 (36)	50 (89)	7.1 (1.2 to 13.4)
Other[b]	143 791	101 961 (1.1)	1095 (0.8)	87 (234)	172 (464)	2.3 (−0.3 to 5.0)

[a] Adjusted for physicians' 2014 opioid prescription claims and change in total drug claims from 2014 to 2015.

[b] Includes (in descending order of total dollars of payments received) psychiatry, emergency medicine, obstetrics/gynecology, otolaryngology, pediatrics, ophthalmology, and dermatology (all with <$100 000 in total payments).

Figure. Opioid Prescription Claims in 2015 for 25 471 Physicians Who Received Any Industry Meals Related to Opioid Marketing During 2014



Analysis excludes 296 (1.1%) of the 25 767 physicians who received opioid marketing in 2014; these physicians received only nonmeal payments. Error bars represent 95% confidence intervals for the estimates.

Methods | We linked 2 US databases. From the Open Payments database, we obtained information on all transfers of value from pharmaceutical companies to physicians ("payments") during 2014.[5] We identified all nonresearch payments involving opioid products, excluding buprenorphine hydrochloride marketed for addiction treatment. From the Medicare Part D Opioid Prescriber Summary File, we obtained information on all claims from physicians who wrote opioid prescriptions (initial or refill) filled for Medicare beneficiaries during 2015.[6] We included all physicians with complete, nonduplicate information who had at least 10 opioid claims during 2015, and matched physicians across databases using name and location.[7]

We analyzed 2015 opioid claims in relation to marketing using multiple linear regression. Covariates included 2014 opioid claims and the change in total drug claims from 2014 to 2015. We also analyzed 2015 opioid claims in relation to opioid-related marketing meals in 2014, adjusting for these covariates and receipt of industry payments other than meals. Claims were $\log_{10}$-transformed to address skewed data. The study was considered exempt by the Brown University Institutional Review Board.

Results | In 2015, 369 139 physicians prescribed opioids under Medicare Part D and met study inclusion criteria. In 2014, 25 767 (7.0%) of these physicians received 105 368 nonresearch opioid-related payments totaling $9 071 976. Only 436 (1.7%) physicians received $1000 or more in total. The 3 companies with the highest payment totals were INSYS Therapeutics (which manufactures Subsys, the fentanyl sublingual spray; $4 538 286), Teva Pharmaceuticals USA ($869 155), and Janssen Pharmaceuticals ($854 251). Marketing included speaking fees and/or honoraria ($6 156 757; n = 3115), meals ($1 814 340; n = 97 020), travel ($730 824; n = 1862), consulting fees ($290 395; n = 360), and education ($79 660; n = 3011). Payments for meals were reported for 25 471 physicians and had a median payment value of $13 (interquartile range, $11-$17).

Total opioid claims for Medicare beneficiaries decreased from 60 055 242 in 2014 to 59 822 155 in 2015 (mean [SD] difference per physician, −0.6 [138.6]). Whereas physicians receiving no opioid-related payments had fewer opioid claims in 2015 than in 2014 (mean [SD] difference, −0.8 [114.4]), physicians receiving such payments had more opioid claims (mean [SD] difference, 1.6 [317.1]). In multivariable modeling, receipt of any opioid-related payments from industry in 2014 was associated with 9.3% (95% CI, 8.7%-9.9%) more opioid claims in 2015 compared with physicians who received no such payments (**Table**).

Each meal received in 2014 was associated with an increasing number of opioid claims in 2015 (**Figure**). In multivariable modeling, each additional meal was associated with an increase of 0.7% (95% CI, 0.6%-0.8%) in opioid claims.

Discussion | Of physicians who prescribed opioids under Medicare Part D, 7.0% received nonresearch payments related to opioid products in 2014. These payments were associated with greater opioid prescribing in 2015. One company, INSYS Therapeutics, accounted for 50% of the nonresearch payments.

Our findings add to prior studies of industry marketing to physicians by examining receipt of payments in 1 year and prescribing in the subsequent year, and adjusting for overall prescribing trends.

Limitations include the possibility of reverse causality because physicians who receive industry payments may be predisposed to prescribe opioids. Our findings establish an association, not cause and effect.

Amidst national efforts to curb the overprescribing of opioids, our findings suggest that manufacturers should consider a voluntary decrease or complete cessation of marketing to physicians. Federal and state governments should also consider legal limits on the number and amount of payments.

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Published Online: May 14, 2018. doi:10.1001/jamainternmed.2018.1999

Author Contributions: Drs Hadland and Li had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hadland, Cerdá, Marshall.
Acquisition, analysis, or interpretation of data: Hadland, Li, Krieger, Marshall.
Drafting of the manuscript: Hadland.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hadland, Li, Krieger, Marshall.
Administrative, technical, or material support: Hadland, Krieger, Marshall.
Study supervision: Hadland, Cerdá, Marshall.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Hadland was supported by the Thrasher Research Fund Early Career Award, the Academic Pediatric Association Young Investigator Award, and the Loan Repayment Program Award L40 DA042434 (National Institutes of Health/National Institute on Drug Abuse [NIH/NIDA]). Dr Cerdá was supported by R01 DA039962 (NIH/NIDA).

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Jesse Yedinak, MPA, Brown University School of Public Health, provided research and administrative assistance. Sandra Galea, MD, DrPH, Boston University School of Public Health, David Fiellin, MD, Yale University School of Medicine, and Jason Vassy, MD, MPH, SM, VA Boston Healthcare System and Harvard Medical School, reviewed the manuscript. No compensation was received for these contributions.

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COMMENT & RESPONSE

Caution to Readers About Systematic Review on Vitamin K and Prevention of Fractures That Included Problematic Trials

To the Editor On behalf of my coauthors, I write to alert readers about the following article, "Vitamin K and the Prevention of Fractures: Systematic Review and Meta-analysis of Randomized Controlled Trials."[1]

In this systematic review and meta-analysis,[1] we assessed whether oral vitamin K (phytonadione and menaquinone-4) supplementation was associated with a reduction in bone loss and prevention of fractures. We included 13 trials with data on bone loss, and 7 of these trials reported fracture data. We reported that all studies but 1 showed an association of phytonadione and menaquinone-4 with reduction of bone loss. All 7 trials that had reported data on fractures were Japanese and used menaquinone-4. We reported: "Pooling the 7 trials with fracture data in a meta-analysis, we found an odds ratio (OR) favoring menaquinone-4 of 0.40 (95% confidence interval [CI], 0.25-0.65) for vertebral fractures, an OR of 0.23 (95% CI, 0.12-0.47) for hip fractures, and an OR of 0.19 (95% CI, 0.11-0.35) for all nonvertebral fractures."[1(p1256)] We concluded: "This systematic review suggests that supplementation with phytonadione and menaquinone-4 reduces bone loss."[1(p1256)]

However, our systematic review[1] included reports of 3 trials authored by Sato et al.[2-4] These 3 trials have been cited by Bolland and colleagues[5] as being problematic, and 2 of the trials[3,4] have been retracted. At the time of our analysis, we undertook a sensitivity analysis excluding those 3 trials (Figure 4 in our article), which resulted in the differences in hip fracture effectiveness being no longer statistically significant.[1]

As we reported in the Results section of our original article, "Because 1 of the centers provided most of the data for hip fractures and this center had included populations with a very high fracture risk,[33-35] we undertook a sensitivity analysis excluding data from this center. The OR for hip fractures for the remaining 2 studies when combined was 0.30 (still a large effect); however, this finding was no longer statistically significant (95% CI, 0.05-1.74; P = .18) (Figure 4)."[1(p1258)]